Message

**From**: Cynthia Van Landingham [cvanlandingham@ramboll.com]
**Sent**: 11/22/2019 9:26:33 PM
**To**: Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]
**CC**: Jerry Campbell [JCampbell@ramboll.com]; Harvey Clewell [HClewell@ramboll.com]; Robinan Gentry [rgentry@ramboll.com]; Walsh, Patrick [patrick-walsh@denka-pe.com]; Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]; Jones, Samantha [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eac77fe3b20c4667b8c534c90c15a830-Jones, Samantha]; Lavoie, Emma [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=86ac7844f12646c095e4e9093a941623-Lavoie, Emma]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Kirby, Kevin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cbb65672f6f34545be460a66ff6fa969-Kirby, Kevin]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Morozov, Viktor [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=03cc9abb639c453fabc2bbb3e4617228-Morozov, Viktor]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; White, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4e179825823c44ebbb07a9704e1e5d16-White, Paul]; Hawkins, Belinda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=075561d171e845828ec67a945663a8e6-Hawkins, Belinda]
**Subject**: RE: Chloroprene PBPK: metabolic parameters / IVIVE calculations

Paul
Below are Ramboll's responses to the comments/questions you provided in your e-mails of Nov. 18th and 19th. We appreciate your careful review and have supplied you with our comments in bold and Italics following each of your comments (bulleted by each email). This will complete addressing all of the questions that Ramboll has received to date. If you have any additional comments/questions, please let us know.

Thanks,
Cynthia

E-mail from Paul Schlosser – November 18, 2019 1:38 PM CST

- While I can't speak to the ultimate numerical significance, there are a number of discrepancies in and among the descriptions and calculations for IVIVE of metabolic parameters (i.e., between statements in the main report, p. 9, Supp Mat C, and the spreadsheet, Supp Mat D), and a couple of choices that I'm questioning. See below.
  I would need to request a copy of Houston and Galetin (2008), which might take a few days, so it would help if Ramboll can send a copy.
  ***Ramboll Response: Paper sent by email 11/18/2019***

- I've highlighted the items that seem most significant, where corrections in the IVIVE spreadsheet appear to be needed or the justification (40 vs. 45 mg/g microsomal protein in rat liver) seems a bit weak. A copy of the spreadsheet where I've highlighted cells of concern is attached.
  Metabolic parameters and IVIVE extrapolation

The following are found in the spreadsheet, EPA Supp Mat D, in the "IVIVE" tab.

- **BW values for mice and rats, cells C22-C25**: these differ from the standard BW values listed in table S-1. For the sake of consistency, and since the tissues used to obtain microsomes were likely from juvenile/young adult animals, it might be better to use the lower, standard BW values from Table S-1. Alternately the Supp Mat C, Table 1 (which match the values in the Supp Mat D, IVIVE table), should be used in the model code for dose calculations in the absence of study-specific values.

***Ramboll Response: Body weight values in the spreadsheet, EPA Supp Mat D, in the "IVIVE" tab are now mouse F 0.04, M 0.04; Rat F 0.26, M 0.4; Human 70. The change in body weight for the female mouse and male and female rat were made to match the weighted averages over the two year bioassay for the control animals in the NTP Survey. These recommended values will also be changed in Supp Mat C, Table 1.***

- **Liver and lung microsome content,** cells G22-G27 (liver) and cells H22-H26 (lung in all species):
- **Mouse liver:** From Supp Mat C, value of 35 mg/g is from Medinsky et al. (1994), so reference in cell G27 is incorrect (says "rat value used for mouse")

***Ramboll Response: The citation in the spreadsheet should be Medinsky et al. (1994) – we will correct***

- **Rat liver:**
  - report p. 9 says 45 mg/g used for rats, not consistent with 40 in IVIVE spreadsheet (cells G24-25);

***Ramboll Response: The value of 40 used is the average between the value used for rats in Medinsky et al. (1994) of 35 and the value in Houston and Galetin (2008) of 45 – as reported in Table 1 of Supp Mat C. The reference in Supp Mat D has been changed to reflect that.***

- need to obtain Houston and Galetin (2008);
  ***Ramboll Response: Paper sent by email 11/18/2019***

- Supp Mat C says an average of values for rat from Medinsky et al. (1994) (sentence is confusing, "For mouse, 35 mg/g liver was reported by Medinsky et al. (1994) for both rat and mouse,") and 45 mg/g from Houston and Galetin, but it's not entirely clear why a cross-species average would be used for the rat, but not the mouse ; if Medinsky et al. (1994) also measured 35 mg/g from rat liver, then an average may make sense…
  ***Ramboll Response: The value used by Medinsky et al. (1994) for both rats and mice was 35 mg/g liver. We have clarified this in Supp Mat C.***

- In Barter et al. (2007), Figure 2, part A, there appear to be many papers reporting 45 mg/g for the rat, so the value of 45 mg/g may be better supported;
  ***Ramboll Response: 40 mg/g is a more representative value due to the more robust data available in the human and the likelihood that MPPGL in rat and human is similar.***

- reference in cell 27 just cites Houston and Galetin (2008), not consistent with "40".
  ***Ramboll Response: Reference in cell G27 is updated to reflect the reference reported in Supp Mat C***

- **Human liver:**

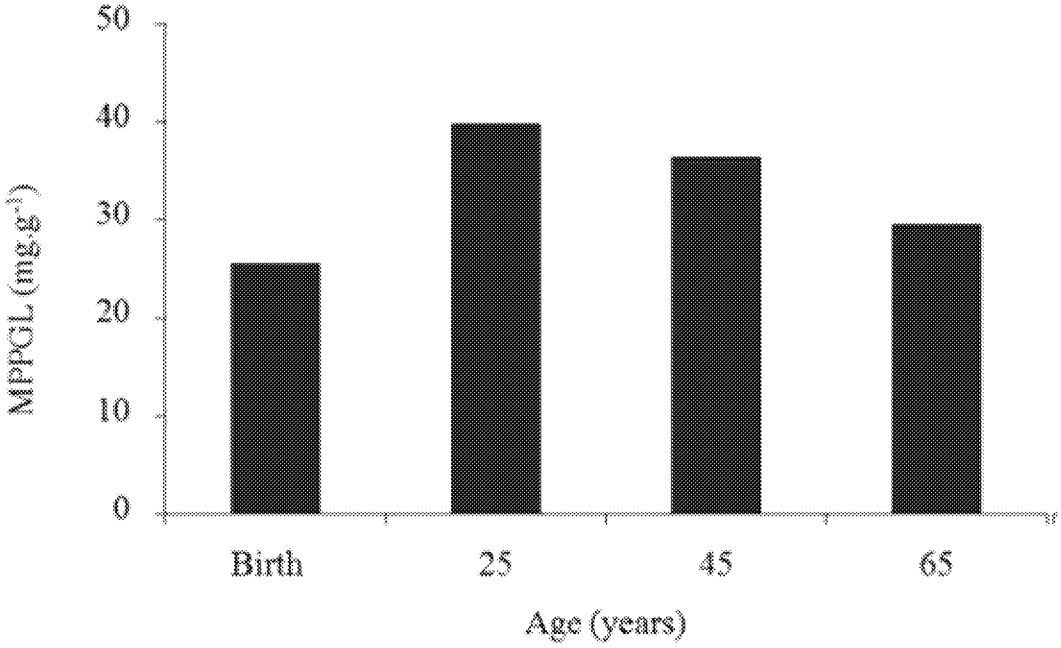
- Text in main report, p. 9, says 40 mg/g, which matches the value listed in Supp Mat C;
- *But* IVIVE cell G26 has **50** mg/g;

***Ramboll Response: We agree this value should be 40 and it will be corrected.***

- Supp Mat C, "Based on their meta-analysis and consensus report of the human data (Barter et al., 2007), 40 mg/g liver is recommended for human adults for chloroprene IVIVE-PBPK modeling," so it would be less confusing if the main report and IVIVE cell G27 cited this reference, not Barter et al. (2008)

***Ramboll Response: The citations will be updated in Supp Mat C, Supp Mat D and the main document.***

- From Barter et al. (2007): "Values of MPPGL were approximately 36 and 31% lower in newborn and elderly (80 years) individuals than those in a 25-year-old individual (typically the age of individuals used in clinical pharmacology studies). The use of a value of MPPGL of 40 mg $g^{-1}$, determined for a young adult, would be expected to result in an overprediction of clearance in very young or very old patients. Therefore, MPPGL values relevant to the age of the population in which predictions are being made should be used in IVIVE." Image below is from Barter et al. (2008). Should risk assessment be focused on young adults, or entire population; i.e., use more of a population-average value from this reference? The young-adult value of 40 mg/g likely will be most health-protective.
    - But the statement in Supp Mat C appears to mis-represent the conclusions of Barter et al. (2007): it should be made clear that this value is the recommendation of the model authors, not the cited paper.




***Ramboll Response: Supp Mat C is a report that was prepared for Ramboll by an expert on IVIVE, Dr. Miyoung Yoon. This report provides the details of Dr. Yoon's critical review of the literature to provide recommendations for any updates needed to the previously published IVIVE methods applied by Himmelstein et al. (2004) and Yang et al. (2012) in the application of the chloroprene PBPK model for risk assessment. Dr. Yoon is a recognized expert with numerous peer-reviewed publications as primary, contributing or senior author in PBPK modeling (Yoon et al. 2019; Song et al. 2018; Ramoju et al. 2017) and in the development and application of IVIVE methods (Mallick et al. 2019; Song et al. 2019, 2017; Yoon and Clewell 2016; Campbell et al. 2015; Yoon et al. 2014, 2015). In addition, her recommendations for IVIVE methods have been accepted by other USEPA programs for use in the PBPK models for pyrethroids and carbaryl. Dr. Yoon is currently at the USFDA where she is***

***continuing to lead research efforts in this area. The term "recommend" is used throughout the document to provide the opinion of Dr. Yoon. We subsequently invited Dr. Yoon to be an author on the manuscript due to the importance of her contributions.***

- **Lung:** value of 23 mg/g in cells H22-26 does match Himmelstein et al. (2004b), but text in the report says 20 mg/g, and this is the conclusion after some discussion in Supp Mat C. Hence it appears that the value in the IVIVE tab (used) should be 20 mg/g and the reference in cell H27 should be changed to Medinsky et al. (1994).
  ***Ramboll Response: This discrepancy will be corrected.***

- **In Vitro Values of KFLUC for female rat (cell V33) and male rat (cell V38)**: These cells have calculations which are not explained and do not take values from the in vitro metabolic results; e.g., "=1.2/(0.82*2)/1000" in cell V33, which should be just equal to Parameter Summary cell I18.
  ***Ramboll Response: We agree and this discrepancy will be corrected.***

E-mail from Paul Schlosser November 18, 2019 3:42 PM CST

- The other thing I'll need to unpack a bit more tomorrow, are the values/source for mouse liver and lung microsomal protein. Medinsky et al. (1994) did not measure the values they used, and as best I can tell the "numerous" sources they cite are only 4, from rabbits (2) and humans (2). I think the mouse values should be based on studies which actually measured microsomal content in that species. I may have missed the actual citations in Medinsky, but I only see the value in a figure legend, with no citation, and at one point in the discussion, with the 4 non-mouse citations. (Maybe those papers have mouse data in them too, just not in the title?)
  ***Ramboll Response: We were not able to identify the sources of the values reported in Medinsky et al (1994). However, we have relied upon the recommendations of Dr. Yoon for these values.***

E-mail from Paul Schlosser – November 19, 2019 10:10 AM CST

- Some more details on Medinsky et al. (1994):
  The experiments performed/reported are measurements of partition coefficients for butadiene and in vivo gas uptake studies. They did not measure or report microsomal protein fractions and the in vitro kinetics used were taken from Csanady et al. (1992).
  - Csanady et al. (1992) report, "Mouse, rat and human liver microsomal concentrations were 11.6, 16.8 and 14.5 mg/g liver respectively," which both Medinsky et al. and the Ramboll authors conclude are too low, represent poor experimental recovery. I agree with the conclusion, given the large amount of contradicting data for rat and human at least.
  - The description of the PBPK model methods in Medinsky is very brief, does not mention the MPPGL. It is stated in footnote "a" of Table II as, "Liver and lung microsomal concentrations used to extrapolate to in vivo were 35 and 20 mg/g tissue, respectively." No citation there.
  - On p. 1337 in the Discussion, left column, there is a paragraph on the scaling.
    - They cite a paper by Kohn and Melnick that attempted to use the measured MPPGL from Csanady, and found that this under-predicted the measured rate of gas uptake.
    - The "numerous investigators" (4 citations, 2 for rabbit, 2 for human) was only to note that microsomal protein recovery can vary from 50% for the liver to 8-15% for the lung. So it's fine if those are from other species, appropriately makes the point, but 4 papers isn't exactly "numerous".

- They then state, "The values that we used for liver [35 mg/g] was very similar to the 30 mg/g used by Johanson and Filser (13)."
- No specific reference for the lung MPPGL, but then…
- "Thus, in order to successfully simulate *in vivo* behavior from *in vitro* experiments, information must be obtained on the actual amount of enzyme present in the intact tissue. It is likely that the amount of enzyme can depend on the nutrition state, age, strain… as well as a number of other factors. Simulating chemical behavior without direct measurement of this value leads to increased uncertainty in model predictions."

- I have to switch gears right now, don't have time to go into Johanson and Filser. But based on this description it appears their MPPGL (and for lung) were selected to fit the model to the in vivo uptake data. My conjecture: A value of 35 for the liver successfully fits the rat data, where there is minimal lung metabolism. Adding 20 mg/g lung for the mouse gives the extra uptake needed to fit the mouse in vivo data, given 35 mg/g for the liver. (Fig 6 shows that for the rat, adding lung metabolism makes no difference, for the mouse it makes the difference between the simulating being above the data and fitting the data pretty well.)
- So what Medinsky et al. (1994) seems to show is that the IVIVE required in vivo data to adjust/fit the MPPGL and MMGLU. Because butadiene and CP are both small VOCs, maybe these numbers from Medinsky are appropriate, but this is not a ringing endorsement for IVIVE. It is then more of a "parallelogram" than IVIVE: using the in-vitro to in-vivo relationship found for butadiene to obtain extrapolation parameters for CP.
- Alternately, data where MPPGL for the mouse is measured/reported independent of in vivo PK data should be obtained. And the value of 20 mg/g for the lung seems doubly sketchy, since I think it's based on setting the mouse MPPGL to 35 (i.e., equal to the value that works for rat butadiene data). Two of those "numerous" citations in Molinsky are for rabbit lung, so maybe those are a reasonable source.

***Ramboll Response: The values in question represent the recommendations of Dr. Yoon and we stand by the recommendations of Dr. Yoon.***

E-mail from Paul Schlosser – November 19, 2019 2:34 PM CST

- This paper does list 45 mg/g as a rat MPPGL (and human as 40 mg/g). However, it's not a primary source of the data, instead citing earlier papers (most or all from Houston). So I will need to check back to those … the process goes back until the primary data are found. Likewise I think it's appropriate to check the sources cited by Medinsky et al.

  I also still need to check that ***in vitro*** model code/scripts reproduce those figures in the paper. Digging into these questions and discrepancies has taken more time than I expected, and I have other work that I really must get back to. So I need to push back my expected completion of the QA. I will try to do by Dec. 6.
  Given some of the issues raised here, I also think we need to see how Ramboll addresses them before we can finalize the charge questions.

  ***Ramboll Response: We will address any additional issues as you send them to us.***

***References for Dr. Yoon's publications***

***Campbell JL, Yoon M, Clewell HJ. 2015. A Case Study on Quantitative in Vitro to in Vivo Extrapolation for Environmental Esters: Methyl-, Propyl- and Butylparaben. Toxicology 332:67-76.***

*Mallick P, Moreau M, Song G, Efremenko AY, Pendse SN, Creek MR, Osimitz TG, Hines RN, Hinderliter P, Clewell HJ, Lake BG, Yoon M. 2019. Development and Application of a Life-Stage Physiologically-Based Pharmacokinetic (PBPK) Model to the Assessment of Internal Dose of Pyrewthroids in Humans. Toxicological Sciences pre-publication.*

*Ramoju SP, Mattison DR, Milton B, McGough D, Shilnikova N, Clewell HJ, Yoon M, Taylor MD, Krewski D, Andersen M. 2017. The Application of PBPK Models in Estimating Human Brain Tissue Manganese Concentrations. Neurotoxicology 58:226-237.*

*Song G, Moreau M, Afremenko A, Lake BG, Wu H, Bruckner JV, White CA, Osimitz TG, Creek MR, Hinderliter PM, Clewell HJ, Yoon M. 2019. Evaluation of Age-Relation Pyrethroid Pharmacokinetic Differences in Rats: Physiologically-Based Pharmacokinetic Model Development Using In Vitro Data and In Vitro to In Vivo Extrapolation. Toxicological Sciences 169(2):365-379.*

*Song G, Van Landingham CB, Gentry PR, Taylor MD, Keene AM, Andersen ME, Clewell HJ, Yoon M. 2018. Physiologically-based Pharmacokinetic Modeling Suggests Similar Bioavailability of Mn from Diet and Drinking Water. Toxicology and Applied Pharmacology 359:70-81*

*Song G, Sun X, Hines RN, McCarver DG, Lake BG, Osimitz TG, Creek MR, Clewell HJ, Yoon M. 2017. Determination of Human Hepatic CYP2C8 and CYP1A2 Age-Dependent Expression to Support Human Health Risk Assessment for Early Ages. Drug Metab Dispos 45(5):46-375.*

*Yoon M and Clewell HJ. 2016. Addressing Early Life Sensitivity Using Physiologically Based Pharmacokinetic Modeling and In Vitro and In Vivo Extrapolation. Toxicol Res 32(1):15-20.*

*Yoon M, Ring C, Van Landingham CB, Suh M, Song G, Antonijevic T, Gentry PR, Taylor MD, Keene AM, Andersen ME, Clewell HJ. 2019. Assessing Children's Exposure to Manganese in Drinking Water Using a PBPK Model. Toxicology and Applied Pharmacology 380:114695.*

*Yoon M, Kedderis GL, Yan GZ, Clewell HJ. 2015. Use of in Vitro Data in Developing a Physiologically Based Pharmacokinetic Model: Carbaryl as a Case Study. Toxicology 332:52-66.*

*Yoon M, Efremenko A, Blaauboer BJ, Clewell HJ. 2014. Evaluation of Simple in Vitro to in Vivo Extrapolation Approaches for Environmental Compounds. Toxicology In Vitro 28(2):164-170.*

**Cynthia Van Landingham**
Senior Managing Consultant

D +1 (318) 3982091
M +1 (318) 6147920
cvanlandingham@ramboll.com

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**From:** Schlosser, Paul <Schlosser.Paul@epa.gov>
**Sent:** Tuesday, November 19, 2019 2:34 PM
**To:** Cynthia Van Landingham <cvanlandingham@ramboll.com>
**Cc:** Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>
**Subject:** RE: Chloroprene PBPK: metabolic parameters / IVIVE calculations

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Given some of the issues raised here, I also think we need to see how Ramboll addresses them before we can finalize the charge questions.

I guess the idea of doing the QA in parallel with the peer review was not a good idea. :-/

-Paul

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**From:** Cynthia Van Landingham <cvanlandingham@ramboll.com>
**Sent:** Monday, November 18, 2019 2:00 PM
**To:** Schlosser, Paul <Schlosser.Paul@epa.gov>
**Cc:** Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>
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Paul,
Attached is the paper that you requested in your e-mail below. I will get back to you as soon as I can with the answers to your other questions.

Cynthia

**Cynthia Van Landingham**
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Metabolic parameters and IVIVE extrapolation

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  - **Mouse liver:** From Supp Mat C, value of 35 mg/g is from Medinsky et al. (1994), so reference in cell G27 is incorrect (says "rat value used for mouse")
  - **Rat liver:**
    - report p. 9 says 45 mg/g used for rats, not consistent with 40 in IVIVE spreadsheet (cells G24-25);
    - need to obtain Houston and Galetin (2008);
    - Supp Mat C says an average of values for rat from Medinsky et al. (1994) (sentence is confusing, "For mouse, 35 mg/g liver was reported by Medinsky et al. (1994) for both rat and mouse,") and 45 mg/g from Houston and Galetin, but it's not entirely clear why a cross-species average would be used for the rat, but not the mouse ; if Medinsky et al. (1994) also measured 35 mg/g from rat liver, then an average may make sense…
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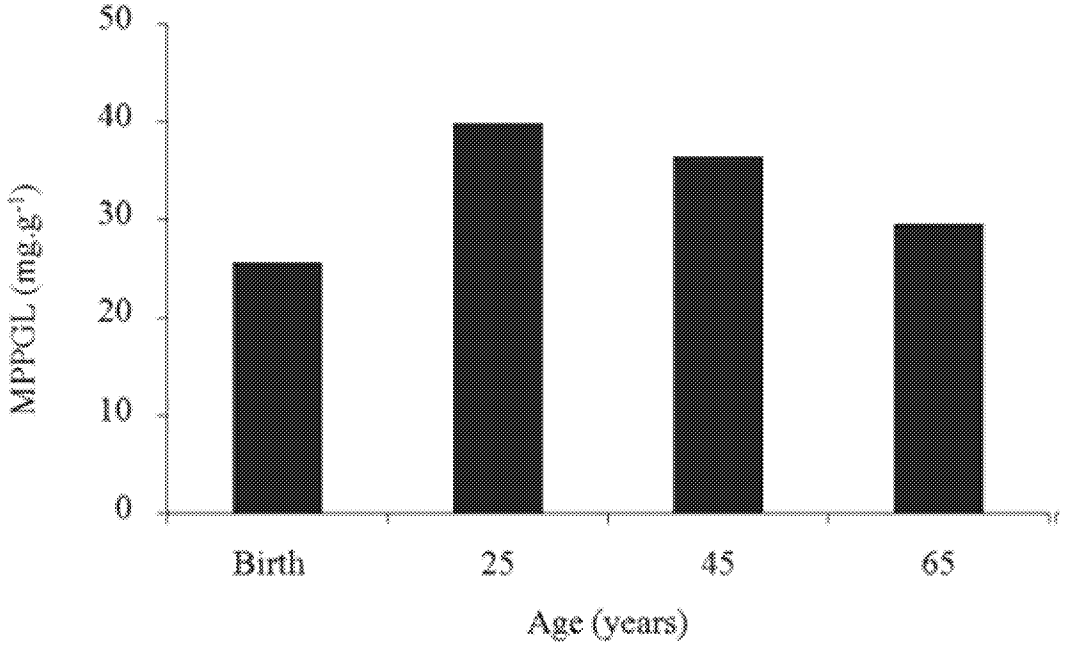


  - **Lung:** value of 23 mg/g in cells H22-26 does match Himmelstein et al. (2004b), but text in the report says 20 mg/g, and this is the conclusion after some discussion in Supp Mat C. Hence it appears that the value in the IVIVE tab (used) should be 20 mg/g and the reference in cell H27 should be changed to Medinsky et al. (1994).

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